

REMARKS/ARGUMENTS

The Office Action mailed December 22, 2005 has been carefully considered and the following response prepared. Claims 14 and 18 have been amended to state that the microorganism is a *Corynebacterium* species. Claims 27 and 28 have been canceled without prejudice. The dependency of claim 29 has been amended to claim 18 in view of the cancellation of claim 28. Claim 15 was amended to correct a minor typographical error.

Applicants' attorney, Liza D. Hohenschutz, would like to thank Examiner Fronda for the courteous telephone interview on March 16, 2005 regarding the present Office Action, in particular, the Restriction Requirement and the rejection under 35 USC 112, first paragraph that the claims are not enabled. Examiner Fronda advised Applicants' attorney to file a response to the present Office Action, and he would consider withdrawing the final status of the Office Action and the Restriction Requirement and issuing another non-final Office Action that included claims 30-40, presently withdrawn from consideration. The substance of the interview is discussed in more detail below.

At page 2 of the Office Action, claims 30-40 were withdrawn from consideration as being drawn to a non-elected invention. The Examiner asserted that claims 30-40, which are directed to methods for producing L-valine using a microorganism having an increase in the activity of *ilvD* as a result of a mutation of the endogenous gene encoding *ilvD*, are unrelated and different from claims 14-29 which are directed to a microorganism that is transformed with the wild type *ilvD* gene and/or *ilvBNC* genes. The Examiner stated that, since Applicant has received an action on the merits for the originally presented invention, claims 14-29 have been constructively elected by original presentation for prosecution on the merits.

Applicants respectfully request withdrawal of the restriction requirement and examination of claims 30-40 in the present application. As discussed with Examiner Fronda during the telephone interview, the subject matter of claims 30-40 was examined in the Office Action mailed April 5, 2004. In the Office Action mailed April 5, 2004, claims 1-17 were examined. The method of claim 30 finds support in the methods of claims 1, 4 and 5, now canceled, especially claim 5 which was drawn to a process for the

microbial production of L-valine in which the endogenous ilvD activity is increased by a mutation of the endogenous ilvD gene which serves to generate corresponding enzymes having increased activity. Claims 31-40, which depend from claim 30, find support in claims 5, 8, 9, 10, 11 and 13, now canceled. The methods of claims 30-40 were thus examined in the previous Office Action mailed April 5, 2004, and should continue to be examined in the present application. Applicants accordingly request withdrawal of the restriction requirement and examination of claims 30-40 in the present application.

At page 3 of the Office Action, the Examiner rejected claims 14-29 under 35 USC 112, first paragraph, for lack of written description. The basis for this rejection is that the specification fails to sufficiently describe the claimed invention in such full, clear concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed genus of ilvD and/or ilvBNC genes from any biological source having any nucleotide sequence and structure. Additionally, the Examiner indicated that the specification failed to provide an adequate written description of regulatory elements and untranslated regions that are essential to the function of each of the recited genes.

Applicants traverse this rejection. In order to satisfy the written description requirement of 112, first paragraph, the Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is claimed. *Vas Cath Inc. v. Mahurkur* 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). One shows that one is "in possession" of the invention by such descriptive means as words, structures, figures, diagrams, formulas, etc. that fully set forth the claimed invention. *Lockwood v. American Airlines* 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

The specification provides an adequate written description of the claimed methods. Applicants disclose the sequence of the ilvD gene from *Corynebacterium glutamicum*. The ilvD gene from *Brevibacterium flavum* was also known (Inui et al. JP 08-089249 cited in the previous Office Action). Genes for ilvBN and ilvC from *Corynebacterium glutamicum* were disclosed in Keilhauer et al. Journal of Bacteriology 175: 5595-5603 (1993). The disclosure of a sequence or other characteristics common to all ilvD or ilvBNC genes is thus not needed in order to describe the genes useful in the claimed methods. If persons skilled in the art desire other sequences encoding ilvBNC or

ilvD, functional complementation as known in the art and exemplified in the specification at pages 6-8, can be used to isolate other ilvBNC and/or ilvD genes.

Additionally, the specification provides adequate written description of regulatory elements and untranslated regions. The ilvBNC and/or ilvD genes can be expressed using the native regulatory elements and untranslated regions naturally associated with the coding region, or a promoter and untranslated region functional in prokaryotes. The specification discloses expression of the genes at page 5, last paragraph through page 6, first paragraph. The specification discloses the ilvD gene (SEQ ID NO: 1) with regulatory, coding and untranslated regions from *Corynebacterium glutamicum* in Example 1. Keilhauer *et al.* Journal of Bacteriology 175: 5595-5603 (1993) discloses the native regulatory elements and untranslated regions of the ilvBNC genes of *Corynebacterium glutamicum*. The specification discloses examples of suitable vectors for expression of the genes at page 8.

Applicants have thus provided an adequate written description of the nucleotide sequences employed in the claims to enable persons skilled in the art to practice the full scope of the invention. Withdrawal of this section 112, first paragraph rejection is requested.

At page 4 of the Office Action, the Examiner rejected claims 14-18 and 20-29 under 35 USC 112, first paragraph as not enabled. This rejection is newly applied. The previous Office Action mailed April 5, 2004 did not contain a rejection under section 112, first paragraph on enablement grounds. The rejection was also discussed during the telephone conference with Examiner Fronda on March 16, 2005. Applicants request withdrawal of the final status of the present Office Action in view of this new rejection of the claims. MPEP 706.07 states that the second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c). The instant section 112, first paragraph rejection was not necessitated by Applicants' response to the previous rejection. Without acquiescing to the appropriateness of the instant section 112, first paragraph rejection, the grounds for the present rejection, discussed in more detail below, were present in claims 1-17 examined

in the first Office action and a rejection could have been made at that time. It is premature to reject the claims for the first time in a final Office Action when the Applicants claim amendments did not make the rejection necessary.

In rejecting the claims 14-18 and 20-29, the Examiner stated that the specification, while being enabling for an isolated microorganism transformed with a gene construct containing SEQ ID NO: 1 and SEQ ID NO: 2 and a method for producing L-valine using the isolated microorganism, does not reasonably provide enablement for any other embodiment. The Examiner indicated that it would require undue experimentation to make the microorganism employed in the claimed methods because the amount of experimentation required to screen, search and isolate *ilvD* and/or *ilvBNC* genes from any microorganism and transforming them into any microorganism where the activity of any *ilvA*, *panB*, *panC*, *panE* and *panD* enzymes is reduced or eliminated and determining whether the microorganism can still produce L-valine. The Examiner further indicated that it cannot be predicted whether or not any *ilvD* or *ilvBNC* gene from any biological source can be functionally expressed in any microorganism and still produce L-valine and Zhou *et al.* Protein Expr. Purif. 34(1): 87-94 (March 2004) to support the assertion that organisms have specific codon preferences, and that eukaryotic genes and polynucleotides often do not express in prokaryotic host cells because of different codon usage.

Applicants traverse this rejection. Claims 14 and 18 and 30 have been amended to state that the microorganism is a *Corynebacterium* species.

In order to make a rejection under section 112, first paragraph, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of section 112, first paragraph unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. It is incumbent upon the Examiner, whenever a rejection on this basis is made, to explain why he doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of his

own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Enablement is not precluded by the necessity for experimentation. However, experimentation needed to practice the invention must not be undue experimentation. The key word is “undue” not “experimentation”. The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988).

The instant specification provides guidance at pages 6-8 for isolating genes using functional complementation. The method at pages 6-8 of the specification was used to isolate *ilvD* from *Corynebacterium glutamicum* and can be used to isolate other genes or genes from other microorganisms. The specification also discloses methods for deleting all or a part of genes in microorganisms, such as the *ilvA* and *pan B* and *C* genes, and methods for identifying such microorganisms at pages 8-10. Additionally, Example 1 shows isolation of the *ilvD* gene from *Corynebacterium glutamicum* using functional complementation. Examples 2 and 4 show the construction of *ilvA* and *panBC* deletion mutants of *Corynebacterium glutamicum*. Example 5 shows expression of the genes *ilvD*, *ilvBN* and *ilvC* in *Corynebacterium glutamicum*. Although screening is involved in some of the methods, such screening is a routine part of the techniques, not undue experimentation. The specification thus provides sufficient guidance for isolating and identifying the microorganisms employed in the claimed methods so that persons skilled in the art can practice the invention without undue experimentation.

The Examiner’s assertion that the claimed methods are not enabled because it cannot be predicted whether or not any *ilvD* or *ilvBNC* gene from any biological source can be functionally expressed in any microorganism and still produce L-valine is pure speculation and unsupported by any evidence. In the event an *ilvD*, *ilvBN* or *ilvC* gene is not satisfactorily expressed, persons skilled in the art would know that codon usage could

Serial No. 09/914,006

Atty No. 5899*13

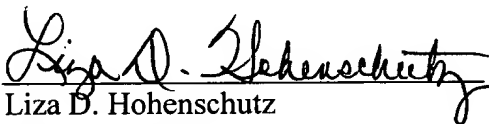
be optimized, as shown by Zhou et al., to overcome problems associated with differing codon usage.

The disclosures of the specification allow persons skilled in the art to practice the invention as claimed without undue experimentation. Withdrawal of this section 112, first paragraph rejection is requested. Applicants also again request the Examiner to withdraw the final status of the present Office Action for the reasons discussed above.

In view of the above, the present application is believed to be in a condition ready for allowance. Entry of the amendments to claims 14 and 18 is requested. These amendments place the claims in condition for allowance or at least in better form for appeal. Reconsideration of the application is requested and an early Notice of Allowance is earnestly solicited. Additionally, withdrawal of the restriction requirement and the final status of the Office Action as discussed above is requested.

Respectfully submitted,
CONNOLLY BOVE LODGE & HUTZ LLP

Date: March 22, 2005

By: 
Liza D. Hohenschutz
Reg. No. 33,712
P.O. Box 2207
Wilmington, Delaware 19899
Attorney for Applicants

LDH/alh/354610